REMARKS

This amendment is responsive to the Office Action mailed January 26, 2011. Claims 9, 10, 12-17, and 26-27 are pending. Claims 15-17, and 26-27 have been withdrawn.

Claim 9 has been amended herein. Specifically, the preamble of Claim 9 has been amended to delete the reference to the objected-to term "isomeric". Support for the amendment is apparent from the original claim.

No new matter is presented.

Restriction/election

Applicants acknowledge the Examiner's imposed election of a species of method (to be searched along with the claims to the compositions) to be selected from:

Group A (Claims 13-14) -- drawn to methods of treating a hyperproliferative disorder;

Group B (Claims 15-16) -- drawn to methods of treating viral infection;

Group C (Claim 17) -- drawn to methods of treating alopecia; and

Group D (Claims 26-27) -- drawn to methods of inhibiting cyclin-dependent kinase or treating cyclin-dependent kinase associated disorders.

Applicants confirm the Examiner's summary of the December 30, 2010 teleconference between the Examiner and Applicants' representatives in which the above-referenced restriction/election was discussed. Applicants hereby confirm their election of Group A, i.e., Claims 13-14, directed to methods of treating a hyperproliferative disorder, to be searched with composition Claims 9, 10, and 12, with traverse.

Applicants traverse the imposed species election in view of the fact that the compounds of Claims 9, 10, and 12 (reduced to a single chemical structure in comparison to the original disclosure), does not impose a significant search burden on the Examiner, and the claims are in a form and are of the sort that is properly viewed as relating to a single invention that should not be restricted.

With respect to the methods, Applicants particularly object to the separate classification of Group D (Claims 26-27, directed to methods of inhibiting cyclin-dependent kinase or treating related disorders) as it

is the underlying mechanism of action of the methods of treatment of the other groups. In other words, in the elected species of method of use, i.e., Group A (methods of treating a hyperproliferative disorder), said method as claimed comprises administering a composition of Claim 9, which, as taught in the specification, is an inhibitor of cyclin-dependent kinases. Therefore, practicing the elected methods of treating a hyperproliferative disorder by administering the cyclin-dependent kinase inhibitor of Claim 9 would necessarily be practicing the methods of Group D (Claims 26-27), *i.e.*, inhibiting a cyclin-dependent kinase and treating a cyclin-dependent kinase associated disorder.

Accordingly, Applicants submit that, at a minimum, the claims of Group D (Claims 26-27) be included with the elected claims of Group A for search and examination.

Objection to the Abstract

In the Office Action, the Examiner objects to the Abstract for allegedly not fully and specifically describing the claimed invention. Applicant submits a replacement Abstract herewith, submitted on a separate page in accordance with 37 C.F.R. §1.72. Removal of the objection to the Abstract is requested in view of the amendments herein.

Response to issues presented under 35 U.S.C. §112, first paragraph

(A) Claims 9, 12-14: Isomeric forms thereof

In the Office Action, Claims 9 and 12-14 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner objects to the claims for reciting "isomeric forms" of the recited compounds, stating:

> "The specification, while being enabling for the compound [formula of Claim 9 inserted], its prodrug, tautomeric, pharmaceutically acceptable salt, N-oxide or stereoisomeric form thereof, does not reasonably provide enablement for any "isomeric form" of said product. (Office Action dated January 26, 2011, page 6.)

Applicants note that Claim 9, from which Claims 10, 12-17, and 26-27 ultimately depend, has been amended herein to delete the objected-to reference to "isomeric forms" of the compound of Claim 9. Accordingly, in view of the amendment herein, the rejection of Claims 9 and 12-14 under 35 U.S.C. §112, first paragraph, for lack of enablement is believed to be overcome, and withdrawal of the rejection is respectfully requested.

(B) Claims 13-14: hyperproliferative disorders

Claims 13-14 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Specifically, the Examiner objects to the claims for reciting methods of treatment of "hyperproliferative disorders", stating:

> "The scope of diseases claimed to be treated would be all types of cancerous tumors, ranging from breast cancer, prostrate cancer, lung cancer, etc. Given the scope of the many types of cancerous tumors included within claims 13-14, their varied etiologies, and the diversity of their patient populations, the disclosures in the Specification is insufficient to permit a person skilled in the art to employ a compound "treating all cancers."" (Office Action dated January 26, 2011, page 11.)

Claims 13 and 14 are presented below:

> 13. A method of treating a hyperproliferative disorder, comprising administering to an animal a compound of claim 9 or 10.
>
> 14. A method of inhibiting proliferation of a cell, comprising contacting the cell with a compound of claim 9 or 10.

First, Applicants point out that while Claim 13 is directed to "a method of treating a hyperproliferative disorder", Claim 14 recites "a method of inhibiting proliferation of a cell". Neither claim recites the language "treating all cancers" *as quoted* by the Examiner above.

The main thrust of the Examiner's comments appears to be a concern that the claimed methods may not be *efficacious* in fully curing/preventing the disorders that might be encpassed by the claim terms. Although that is a legitimate concern for other agencies (and patients), it is misplaced here. As the CAFC has stated:

> "The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995).

Simply stated, approval of the Food and Drug Administration is not a prerequisite for finding a treatment useful within the meaning of 35 U.S.C. §112, first paragraph. Only objective enablement is required. As the CAFC has recently clarified:

> "Typically, patent applications claiming new methods of treatment are supported by test results. But it is clear that testing need not be conducted by the inventor. In addition, human trials are not required for a therapeutic invention to be patentable. Our predecessor court, the United States Court of Customs and Patent Appeals, held in *In re Krimmel* that patent applications need not "prove that compounds or other materials which [the applicant] is claiming, and which [the applicant] has stated are useful for 'pharmaceutical applications' are safe, effective, and reliable for use with humans." 292 F.2d 948, 954, 48 C.C.P.A. 1116, 1961 *Dec. Comm'r Pat. 518* (CCPA 1961).

Applicants have identified therapeutic targets, *e.g.*, cyclin-dependent kinases (cdks), for treating hyper-proliferative disorders, and have tested (thus validating the target as an effective anti-proliferative target) the ability of the claimed cyclin-dependent kinase inhibitors to reduce the viability and proliferation of cell lines, including known cancer cell lines. Applicants note that their specification is replete with teachings of the claimed compositions' ability to inhibit proliferation of a cell. For example, the following *in vitro* data showing the effectiveness of compounds of the invention are presented in the specification:

(1) A cell cycle analysis was performed (Assay 1, pages 65-66) to determine the alteration of the distribution of cells across the cell cycle in response to exposure to the Cdk inhibitors of Formula I. The test cells were terminally arrested in G1 and G2 phase, with evidence of apoptosis and endoreduplication.

(2) The compounds of Formula I were evaluated using the National Cancer Institute panel of human tumor cell lines (Assay 2, pages 67-68). Results of the NCI panel assay are represented by two metrics: (1) the Mean-Graph Mid-point, *i.e.*, the average IC50 over the whole cell panel, and (2) the IC50 (μM) of the inhibitory activity of the compound against an adriamycin resistant cell line (ADR-res). The compounds of Formula I exhibited a Mean-Graph Mid-point of < 50 nM and an IC50 of inhibition of growth of ADR-res cells of < 10μM.

(3) The compounds of Formula I were evaluated using the Calcein AM viability assay (Assay 4, pages 69-70) to further measure loss of cellular viability. Cellular IC50's were determined in the human

colorectal carcinoma cell line, HCT-116, and the normal human fibroblast, IMR90. The compounds of Formula I achieved the following results: HCT-116 (<10nM), HCT-116 protein-adjusted (<500 nM), A2780 (<10 nM), IMR90 (<100 nM).

(4) The inhibitory activity of the compounds of Formula I were also measured in kinase biochemical assays, *see* Assay 6, pages 73-76 of the specification.

Furthermore, Applicant's data show that compounds of Formula I exhibit significant anti-tumor activity *in vivo*, *see*, *e.g.*, Assay 7: Xenograft Tumor Models, found on pages 76-78, and Figure 8. Additionally, compounds of Formula I performed at least comparably in *in vitro* assays as compared to other compounds in the genus, and often exhibited superior performance. For example, *see*, Assay 3 (pages 68-69 of the specification), measuring the irreversible loss of viability of human colorectal carcinoma cells after a specified period of exposure to a test inhibitor compound of Cdk. Compound B16 (recited in the claims) exhibited an IC50 of < 100 nM in the assay, and the IC50 was reached within 30 to 60 min at 100 nM (*see*, additionally, Figure 3).

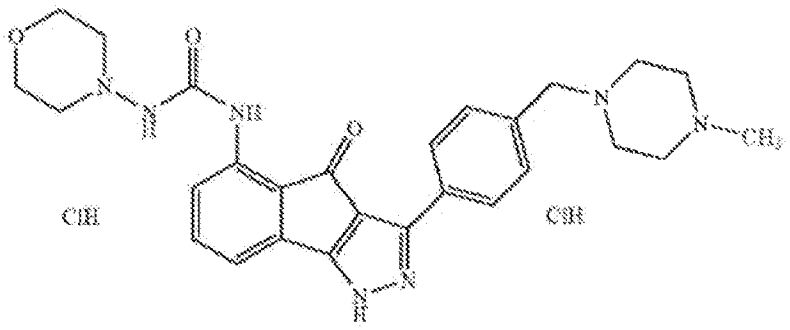
Accordingly, in view of the foregoing remarks and amendments herein, Applicants submit that Claims 9 and 12-14 are definite and enabled and fully comply with the requirements of 35 U.S.C. §112, first and second paragraph. Reconsideration and allowance of Claims 9 and 12-14 are therefore respectfully requested.

Response to issues presented under 35 U.S.C. §103(a)

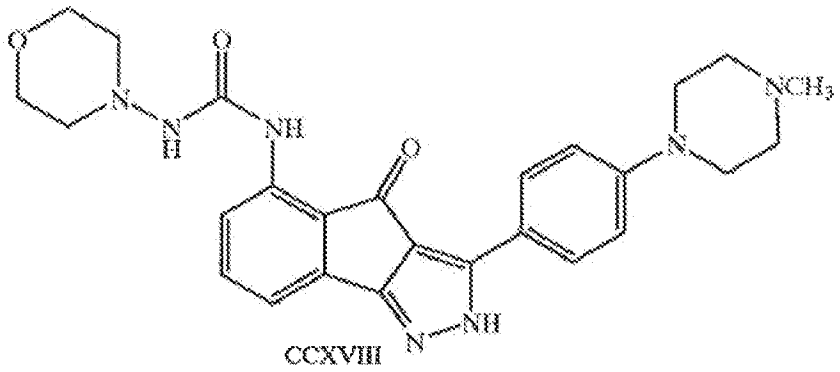
In the Office Action, the Examiner rejects Claims 9-10 and 12-14 as obvious over the combination of Becker et al. (US patent publication 2004/0266854; now US Patent No. 7,605,175) (hereinafter "Becker") in combination with Nugiel et al. (US Patent No. 6,407,103) (hereinafter "Nugiel") and Lima et al., *Current Medicinal Chemistry*, 12: 23-49 (2005) (hereinafter "Lima").

Specifically, the Examiner has identified compound A49 of Becker:

A49



and compound CCXVIII of Nugiel:



CCXVIII

The Examiner notes that Becker and Nugiel differ from the present claims in that they teach N-alkyl substituted piperazine rings (as opposed to the N-alkyl-methoxy substituted piperazine ring in the compounds of Applicants' claims). The Examiner cites Lima as purportedly teaching substitution of -CH_3 by -OR as a bioisosteric replacement. The Examiner then argues that Claims 9-10 and 12-14 are obvious over the combination of Becker and Lima.

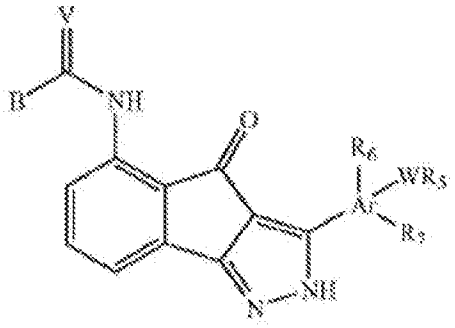
Applicants disagree. First, Applicants point out that in order to modify compound A49 of Becker to arrive at the claimed composition, the methyl group in compound A49 is not substituted simply by an –OR group, **but rather by a $-CH_2-CH_2-O-CH_3$ (or –ROR group).** Accordingly, the teaching of Lima that replacement of $-CH_3$ by –OR is a bioisosteric replacement is of no import, as no mere –OR substitution is sufficient to approximate Applicants' claimed composition.

Furthermore, the Examiner and persons of ordinary skill in the art are well aware that modification or alteration of a structure at any point can drastically change the properties of the structure. For example, taking the Examiner's example of –OR vs. $-CH_3$ (which, as Applicants note above, is not

the case here), even though the groups –OR and $–CH_3$ are isoelectronic, they do posses different physicochemical properties that, without doubt, will have effects on the overall properties of the structure. This is taught even in the Lima citation relied on by the Examiner to suggest a motivation to make bioisosteric replacements toward Applicants' compound: "Some bioisosteric groups dramatically alter the physicochemical properties of substances and, therefore, their activities." (*See*, Lima at p. 25, right column.)

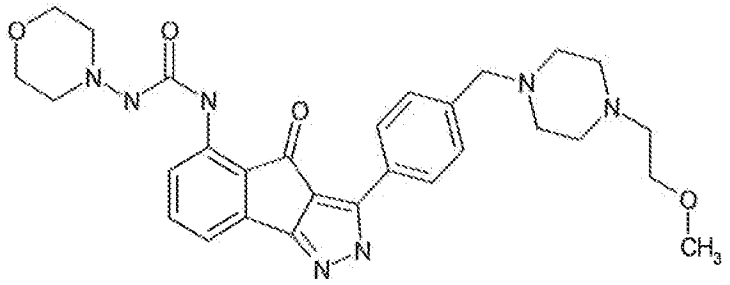
Given the sensitivity of bioactive structures to even slight structural modifications, the Examiner must provide some reason why a person of ordinary skill in the art would have seen a benefit from making the modifications needed to approach Applicants' compound. *KSR International vs. Teleflex*, 82 USPQ2d 1385, 1399 (S.Ct. 2007). In the present case, the Examiner has offered no reason why a person of ordinary skill in the art would have been led to select compound A49 out of the thousands of compounds disclosed by Becker and to further modify that particular compound with an n-alkyl-methoxy substituent at the piperazine ring *and* see that such replacement would have a positive rather than a detrimental effect on the compound's properties. Lima suggests that no such anticipation of a positive result would have been harbored by a person of ordinary skill in the art at the time of the present invention.

Furthermore, in rejecting the claim as obvious over the cited references, the Examiner ignores the fact that in order to even reach the substituent that the Examiner considers to be an obvious modification, that is, N-alkyl-methoxy substituted piperazine, the Examiner has already made multiple individual selections from the virtually infinite listing of possible substituents disclosed in Becker (and Nugiel and Lima). That is, the Examiner ascribes a motivation to a person of ordinary skill in the art to make these individual selections from the base disclosure of the Becker core structure (below).



However, this hindsight selection of pieces from the cited reference to attempt to reconstruct Applicants' invention obviously relies on the Applicant's disclosure for guidance, which is improper. In

order to make the rejection, the Examiner must piece together various selections of the variable moieties from thousands of possible combinations, and even then, the reference fails to fairly teach or suggest Applicant's compounds encompassed by independent Claim 9:



In view of the foregoing, because the art of record fails to show or suggest the compounds and methods of the present invention, Applicants request reconsideration and withdrawal of the rejection of Claims 9-10 and 12-14 under 35 U.S.C. §103(a).

Obviousness-type Double Patenting

Claims 9, 10 and 12 have been rejected under the doctrine of obviousness-type double patenting in view of Claims 1, 4, 6, 10 and 15 of US Patent No. 7,893,057. The referenced patent is broader in scope than the claims of the present application, and whereas claims of US Patent No. 7,893,057 could be said to dominate the invention of the present application, they cannot be said to be directed to the same invention. Nor is it possible that the present application is obvious over the disclosure of US Patent No. 7,893,057, because that patent does not make a disclosure that could be argued to anticipate or suggest the subject matter of present Claims 9, 10 and 12 that speaks from a date prior to the earliest effective priority date of Applicants' claims. (In other words, the subject matter of US Patent No. 7,893,057 that is entitled to an effective date prior to Applicants' earliest priority date relates to a class of compounds that does not anticipate or suggest the compounds depicted in present Claims 9, 10 and 12.)

For the foregoing reasons, Applicants believe the present application and the referenced patent are directed to independently patentable subject matter, and no terminal disclaimer is called for.

Every effort has been made to prosecute this application to allowance. For the reasons set forth above, Applicants believe that all the remaining concerns of the Examiner have been addressed or

obviated. Accordingly, Applicants respectfully request withdrawal of the remaining rejections and allowance of the application.

If Applicants' representatives can be of any further assistance in expediting this case towards allowance, Applicants' representatives would welcome a call at the number below.

Respectfully submitted,

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The undersigned hereby certifies that this correspondence and accompanying documents are being electronically submitted to the U.S. Patent Office under 37 C.F.R. §1.8 on **July 26, 2011**.

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